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A Techno-Legal Study on Current IPR Scenario for Commercialization of Biosimilars in the USA

Chandana N, Madhavi BLR†, Shivanand K Mutta and Shrikanth Pulparambil

Department of Pharmaceutical Regulatory Affairs, Acharya & BM Reddy College of pharmacy, Bengaluru — 560 107, India

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Biologics are essential medical innovations, but they often come at high cost, limiting patient access. Biosimilars provide lower-cost alternatives. However, their entry into the U.S. market is complicated by Intellectual Property Rights (IPR). The Biologics Price Competition and Innovation Act (BPCIA) established an abbreviated pathway for biosimilars, allowing reliance on clinical data from Reference Product Sponsors (RPS). Before IPR reforms, challenging patents was difficult and costly, as granted patents were presumed valid and re-examination processes were often ineffective. The objective of this article is to present, in a nutshell, the IPR scenario related to biosimilars from the perspectives of the patient, the innovator, the regulator, and the biosimilar manufacturers. Biologics and biosimilars are introduced, BPCIA provisions for resolving patent disputes are discussed, some case studies on patent litigation are reviewed, mentioning the patent dance, and Inter Partes Reviews. The article highlights the need for stricter patentability standards to mitigate patent thickets and secondary patenting practices that delay biosimilar market entry, ultimately advocating improved access to affordable biologic therapies and also providing reasonable protection for Biological innovations.

Keywords: BPCIA, Biosimilars, Patent, IPR, Patent Dance, Inter Partes Review, US Patent Laws

Healthcare Industry is constantly evolving with many innovations, one of them being biologics. They make up approximately one-third of the drugs currently in development.[1] Biologics are complex pharmaceutical products derived from living organisms or containing components of living organisms, including vaccines, blood components, gene therapies, and recombinant proteins. They are typically larger molecules that are difficult to characterize than small-molecule drugs and are produced using biotechnology-based methods from natural sources such as humans, animals, or microorganisms. In contrast to most chemically synthesized drugs, which have well-defined structures, biologics are complex mixtures that are difficult to identify and characterize, requiring aseptic manufacturing processes due to their heat sensitivity and susceptibility to microbial contamination.[2]

Biologics are also more expensive and complex to develop and manufacture, taking an average of 10 to 15 years for market entry compared to 7 to 10 years for small-molecule drugs. The manufacturing process for biologics involves five intricate stages: cloning DNA into host cells, fermentation, harvesting, purification, and formulation, often requiring over 250 critical tests, while small-molecule drugs typically require only 40 to 50.

Biologics require significant investment exceeding $2 billion and time as well. Thus, IPR are essential for protecting biologics; however, their high costs can limit patient access, highlighting the necessity of introducing biosimilars, which can offer a more affordable alternative with potential price reductions of 20 to 30%, ultimately saving the U.S. healthcare system more than $133 billion by 2025 and improving access to essential medicines for patients.

Biosimilar products, as defined by the law (42 U.S.C. § 262(i) (2)), are “highly similar to the reference product not withstanding minor differences in clinically inactive components”. A biosimilar is a biological product designed to be similar, but not identical, to an existing approved biologic, known as the reference product. Due to the inherent variability in the complex manufacturing processes of biological products derived from living cells, it is impossible to create an exact replica. Table 1 provides a comparison of the similarities and differences between biologics and biosimilars. All biologics, including the reference product and its biosimilars, exhibit some degree of natural batch-to-batch variation in their physicochemical properties and impurity profiles. This contrasts with traditional generic drugs, which

†Corresponding author: Email: madhaviblr@gmail.com

Table 1 — Comparison of Biologics and Biosimilars: Similarities and differences[8,9]

Characteristics	Biologics	Biosimilars
Definition	Complex drugs produced from living organisms	Highly similar versions of approved biologics, not identical
Similarities		
Primary structure	Unique structure as developed by the innovator	Same as the biologic (identical primary structure)
Indications & Route of administration	Approved for specific indications and routes	May be approved for fewer indications and routes than the biologic
Strength, Dose & Mechanism of action	Defined strength, dose, and mechanism	Same strength, dose, and mechanism of action as the biologic
Biologic activity & Bioequivalence	Proven biologic activity and bioequivalence	No clinically meaningful difference; bioequivalence to the biologic
Purity, Safety, and Potency	Demonstrated for approval	Equivalent purity, safety, and potency as the biologic
Labeling	Specific labeling information	Similar labeling, may vary based on approved indications
Differences		
Special features	Complex molecules produced within living organisms	Similar to biologics, but with minor structural variations
Manufacturing process	Manufactured via proprietary biological processes involving specific cell lines, cell cultures, and purification methods	Manufactured via similar biological processes, but differences may exist in cell lines, culture conditions, or purification methods
Clinical development	Involves full-scale clinical trials (Phases I-III) to establish safety, efficacy, and dosing	Involves tailored clinical trials focused on demonstrating similarity in efficacy, safety, and immunogenicity to the reference biologic
Development period	Takes approximately 15 years to develop	Takes around 8-10 years to develop due to reliance on reference biologic data
Development cost	Approximately $1.2 billion	Ranges between $100-200 million
Patent	Patentable	Non-patentable
Analysis phase	Less extensive analysis	More extensive analysis to prove equivalence
Approval pathway	Biologics license application 351(a)	Biologics license application 351(k)
Approval Requirements	Full report of safety and efficacy investigation	Must demonstrate high similarity to a reference biologic product
Cost of products with examples	Humira (adalimumab)-$ 7,300 for 1 carton (2 pens)	Amjevita- $ 1,558
		Cyltezo - $ 1,500
	Trastuzumab (Herceptin)- $ 7,000 for 1 vial	Herzuma- $ 3,000
	Eculizumab (Soliris)- $ 500,000 per dose	Ultomiris- $ 200,000

are small molecules that can be precisely replicated and considered bioequivalent to their innovator counterparts.[3,4]

The FDA's Center for Biologics Evaluation and Research (CBER) regulates biological products to enhance public health, having approved nine new biologics in the first half of 2023, exceeding the eight approvals in 2022. Over 300 biopharmaceutical products have been introduced in the last forty years, including the 100th monoclonal antibody (mAb) approved in 2021, with forecasts estimating the mAb market to reach $300 billion by 2025. Regulatory approvals for cell and gene therapies have also broadened personalized treatment options for challenging diseases.[5]

The regulations governing biosimilar approval are defined by the BPCIA, which amended the PHS Act to create an abbreviated licensure pathway (section 351(k)) for biosimilars, requiring them to demonstrate biosimilarity to a reference product, while Traditional innovator biologics follow the Section 351(a) Biologics license application (BLA) pathway. However, the complex nature and manufacturing processes of biological products present challenges, particularly regarding IPR, including patents and data exclusivity, which prevents the use of critical safety and efficacy information for a certain period. Additionally, the "patent dance" process, outlined in the BPCIA, addresses patent disputes between reference product sponsors and biosimilar applicants.[6,7]

Segmentation of Biosimilars Market

The global biologics market is valued at approximately USD 511.04 billion in 2024 and is projected to reach around USD 1,374.51 billion by 2033, growing at a compound annual growth rate (CAGR) of 10.4% during this period. Oncology leads the product segment due to increased research and development and technological advancements. The market's rapid growth is driven by an expanding number of studies, innovations in healthcare, and a rising focus on oncology treatments.[10,11]

The biosimilars market on a global scale has been broadly divided based on three main criteria i.e., product, indication and the region.

(i) By product: With regards to product categorization, the market for biosimilars is characterized by recombinant glycosylated proteins, recombinant non-glycosylated proteins, and recombinant peptides. Further, Recombinant glycosylated proteins are divided into monoclonal antibodies, erythropoietin, and others. Similarly, the recombinant non-glycosylated proteins are sub-divided into insulin, granulocyte colony-stimulating factor, recombinant human growth factor, and interferon.

(ii) By indication: Based on the criteria of indication, the global biosimilars market is categorized into chronic diseases, oncology, autoimmune diseases, infectious diseases, blood disorders, growth hormone deficiency, and others.In 2020, the market was dominated by the oncology division. Due to the rising occurrence of cancer and the complexity involved in its treatment, it is estimated that biosimilars used in oncology will dominate the market in the future.

(iii) By the region: Biosimilars are also classified regionally, regional classifications include North America, Europe, Asia Pacific, Latin America, and Middle East & Africa.[12]

Europe holds the title of the global leader in the biosimilars market as this region dominates the market share since 2006 when the first biosimilars were approved. The expert forecast also shows that Europe is likely to remain as a leader in the future as it constitutes over 70% of global biosimilars sales and in addition, Europe also has the highest number of approved biosimilars. These two factors will keep Europe as a pioneer region for sales of biosimilars.[13]

US Biosimilars Market Overview

As of 2023, the FDA has approved a total of 235 therapeutic biologics, which include various biological products such as monoclonal antibodies and therapeutic proteins. In the same year, five new biosimilars were approved, raising the total number of FDA-approved biosimilars in the United States to 45. Notably, 2023 marked a record year for biosimilar launches, with 13 new approvals, including nine for the highly anticipated Humira® (adalimumab). As illustrated in Fig. 1, the data depicts the number of biosimilar approvals and launches from 2015 to 2023.By the end of FY Q3 2024, the FDA has approved an additional 15 biosimilars, bringing the total to 60, with the most recent approval being for Pavblu (aflibercept-ayyh) on August, 2024.[14,15]

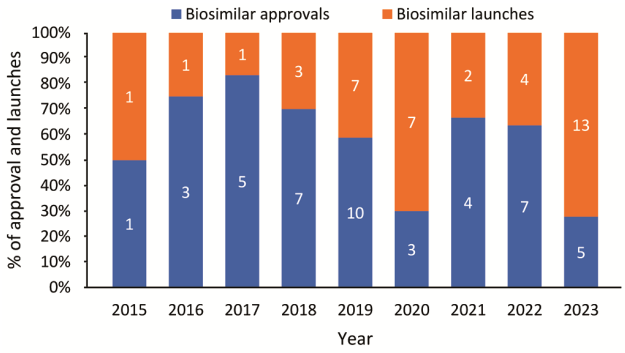

Fig. 1 — Biosimilar approvals and launches[15]

From Fig. 1, it is evident that over the past decade, there has been a significant quantum of research, successful product approvals, and launches in the biosimilars landscape. The U.S. biologics market has grown 12.5% annually, now representing 46% of total spending. Currently, $38 billion is spent on molecules facing biosimilar competition, with another $96 billion targeted by biosimilars in development. Recent biosimilars achieved more than 60% of volume within three years, with non-340B clinics adopting them more than 340B clinics due to reimbursement differences. While the introduction of biosimilars typically increases the use of original products, newer treatments may reduce that volume. By 2027, spending on biosimilars is projected to reach between $20 billion and $49 billion, with total sales estimated at $129 billion over five years, and at least 10 molecules expected to face competition.[16]

The Role of IPR in Commercialization of Biologics and Biosimilars

IPR play a multifaceted role in the development and commercialization of biologics and biosimilars. On the one hand, IPR can serve as a catalyst for innovation by providing incentives for companies to invest in research and development. This encourages the creation of new and improved biologics. On the

other hand, IPR can also act as a barrier to market entry for biosimilars, delaying their availability and potentially limiting competition. This can lead to higher prices for patients and reduce access to affordable medications.[17]

The patenting of biologics involves a complex landscape compared to traditional patent requirements like novelty, utility, and nonobviousness. While the United States Patent and Trademark Office (USPTO) prohibits patents on natural phenomena and abstract ideas, landmark court cases have shaped the eligibility of biologics for patent protection. A notable case is the 1900 case involving epinephrine, which established that isolated and purified compounds from nature could be patented. In 1980, the Supreme Court affirmed that anything made by man, such as recombinant bacteria, is patentable. However, the 2013 Supreme Court ruling in *Association for Molecular Pathology* v *Myriad Genetics Inc.* determined that naturally occurring genes are not patentable, though synthetic products like cDNA can be patented if separated from their natural counterparts. These rulings compel researchers and companies to focus on designing nonnatural variants, combinations, and specific formulations to navigate the complexities of patent eligibility in biologics.[18]

From the above section, it can be observed that there is a rise in the biosimilar market presence in USA. The parameters affecting biosimilar market entry are discussed below.

IPR as a Barrier to Biosimilar Market Entry

Legal barriers to biosimilar entry primarily arise from the complexities associated with IPR. Biosimilar manufacturers face significant challenges in navigating the patent landscape due to the overwhelming number of patents protecting originator biologics, which complicates patent identification and increases the risk of infringement. The lack of efficient mechanisms for identifying relevant patents creates uncertainty for developers, while broad patent claims can obstruct fundamental scientific processes essential for biosimilar development. Additionally, unlike small-molecule drugs, originator biologic manufacturers are not required to disclose their patents to the FDA, further hindering biosimilar manufacturers in assessing potential infringement risks. Although trade secrets related to manufacturing processes are perceived as manageable, they still present substantial challenges due to the inherent complexity and variability in producing biologics.

Regulatory barriers also pose significant obstacles to biosimilar market entry, primarily due to a lack of clarity and uniformity in approval requirements. Biosimilar manufacturers often encounter ambiguity regarding how to meet regulatory expectations, leading to uncertainty in the approval process. This situation is exacerbated when manufacturers opt for parallel development paths rather than sequential ones, which can result in delays and increased costs if they fail to engage with regulators early enough. Furthermore, despite demonstrating similarity to reference products, some biosimilars are still mandated to undergo clinical trials for approval, which can further delay market entry. The differences between regulatory agencies, such as the FDA and EMA, create additional complexity, as manufacturers must navigate varying requirements across jurisdictions. Additionally, many perceive the FDA as more stringent than the EMA, raising concerns about meeting regulatory standards in the U.S. market.[19,20] Figure 2 highlights the key barriers to biosimilar entry in the U.S. market, emphasizing the challenges faced by Biosimilar manufacturers in gaining regulatory approval and market access.

Patent Thickets and Secondary Patenting

Patent thickets in the pharmaceutical industry, particularly for biologics, involve the strategic filing of numerous secondary patents to extend market exclusivity and prevent biosimilar competition. These secondary patents often cover minor variations such as new formulations, routes of administration, or dosages, creating a dense web of protections that biosimilar manufacturers must navigate to avoid

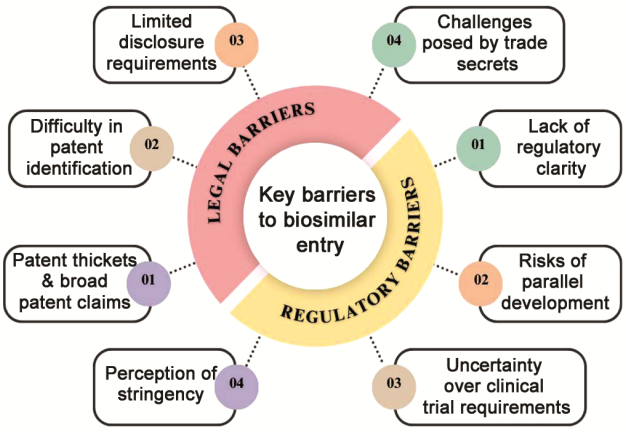

Fig. 2 —Key Barriers to Biosimilar Entry in the U.S. Market[19,20]

infringement. This tactic delays the entry of cost-saving biosimilars into the market, harming patients and payers by maintaining high drug prices. A notable example is Humira (adalimumab), for which 247 patents were filed in the U.S. compared to just 76 in Europe, delaying biosimilar entry until 2023, seven years after its primary patent expired. Similarly, Enbrel (etanercept) has seen at least 57 U.S. patent applications, with biosimilar entry potentially delayed until 2029 due to ongoing litigation. Patent thickets in the U.S. are particularly pervasive compared to Europe; for instance, between 2014 and 2020, 279 patents were asserted in the U.S. for 20 biosimilars, compared to just 16 in the U.K. and one in Germany. These practices have cost U.S. patients and payers an estimated $7.6 billion from 2012 to 2018, and, if unchecked, may become increasingly common, further delaying biosimilar access and competition.[21,22]

Regulatory Exclusivity for Reference Products

Under Section 351(k)(7) of the PHS Act, the FDA cannot approve a biosimilar or interchangeable product application (351(k) application) until 12 years after the initial licensure date of the reference product under Section 351(a). This includes a "data exclusivity" period of 4 years, during which submissions for biosimilar applications are prohibited, and a "market exclusivity" of 12 years, preventing biosimilar approvals.

If certain criteria are met, a "pediatric exclusivity" of 6 months may apply, and for rare diseases, a biologic cannot be licensed for that indication until either the seven-year "orphan drug exclusivity" or the 12-month market exclusivity period expires, whichever is later.

The determination of the first licensure date under Section 351(k)(7)(C) of the PHS Act is critical, as it sets the timeline for the reference product's exclusivity and directly impacts the eligibility of biosimilars or interchangeable biologics for review and approval.[23,24]

Accelerating Market Access: Key Provisions for Biosimilar Approval

In an attempt to address the high cost of biologics, Congress passed the BPCIA of 2009, similar to the Hatch Waxman Act of 1984, which created an abbreviated FDA approval pathway for biosimilars, the equivalent of generic drugs for biologics.[25]

The BPCIA amended the Public Health Service (PHS) Act and creates an abbreviated licensure pathway (section 351(k) of the PHS Act) for biosimilar. Traditional approval for innovator biologics follows the Section 351(a) BLA pathway, Biosimilars follow a specialized route, the Section 351(k) abbreviated Biologics License Application (aBLA), where they must demonstrate biosimilarity to a reference product as defined by 42 U.S.C. § 262(i)(2) for approval.The approval process involves submitting an abbreviated biological license application (aBLA), which relies on comparative data from analytical studies, animal studies, and clinical studies to establish biosimilarity. This approach reduces the need for extensive clinical trials compared to those required for new biologics, thereby lowering development costs and facilitating faster market access while maintaining rigorous safety and efficacy standards.[26] Figure 3 illustrates the biosimilar approval pathway and the patent dance timeline.[30]

The BPCIA aimed to strike a balance between encouraging innovation and protecting consumer interests. It accomplished this by allowing biosimilar manufacturers to utilize certain clinical trial data from an approved reference product. Additionally, it granted the innovator twelve years of exclusivity and established procedures for efficiently resolving patent disputes.

Biosimilar Patent Ligation

Biosimilar patent litigation refers to legal disputes that arise between the manufacturer of a biosimilar referred to as the biosimilar applicant (BA) or 351(k) applicant and the manufacturer of the original reference biologic product known as the Reference Product Sponsor (RPS)regarding patent issues.

The BPCIA has a structure that includes numerous information exchanges between the RPS and the 351(k) applicant, along with two distinct phases of patent litigation commonly referred to as the "patent dance." [27]

Patent Dance

The patent dance, established by the BPCIA, outlines a method for resolving patent disputes between the Reference Product Sponsor (RPS) and biosimilar applicants (BA) during the abbreviated Biologic License Application (aBLA) process. It involves multiple steps of information sharing between the RPS, who owns the referenced drug, and

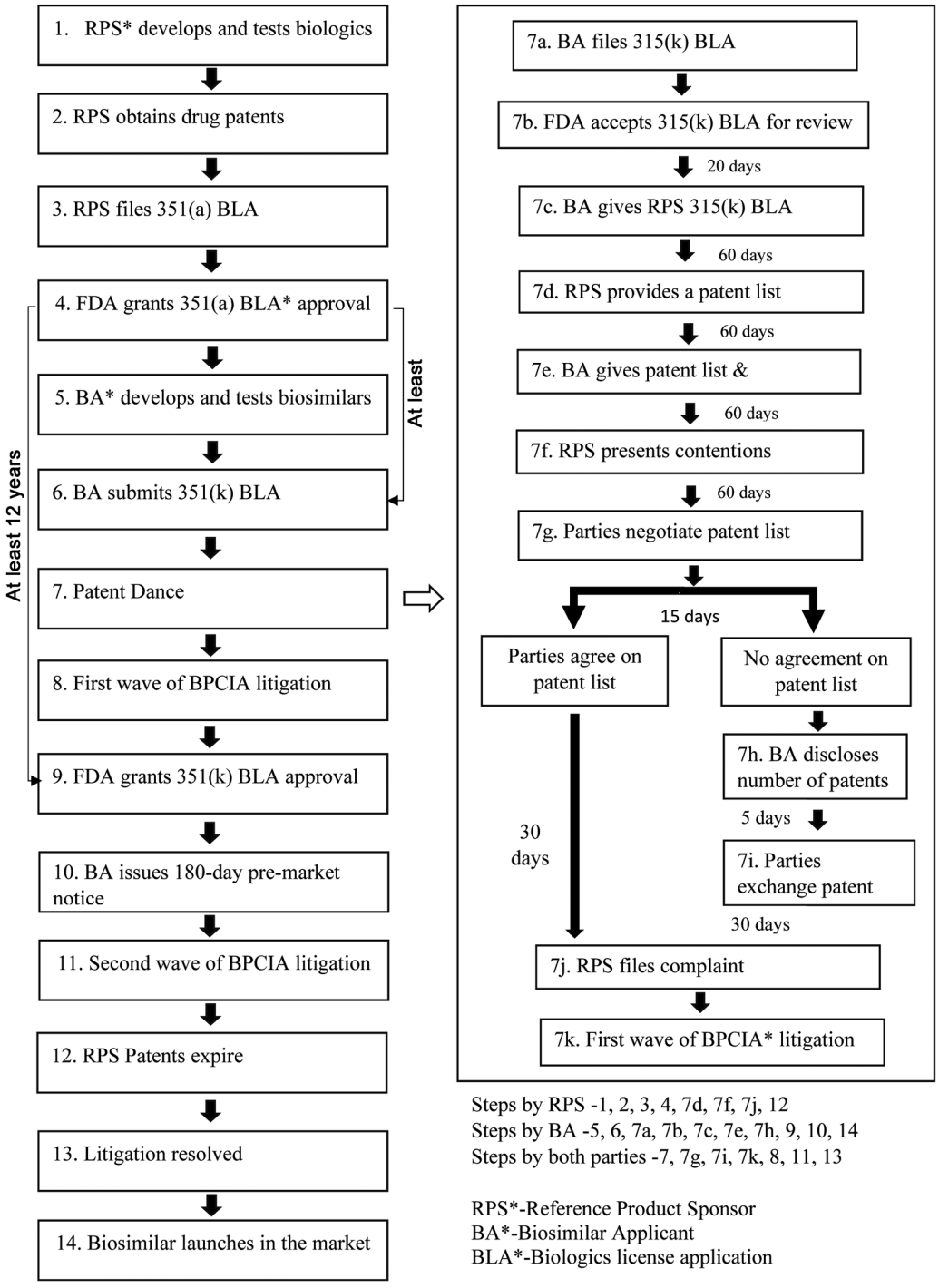

Fig. 3 — Biosimilar Approval Pathway and Patent Dance Timeline[30]

the aBLA applicant. The goal is to streamline the patent litigation process, reducing time and expenses by proactively limiting the scope of potential disputes. By sharing details such as the aBLA, manufacturing methods, and notifying potential patents for initial pre-launch litigation, this patent dance aims to confine the scale of disagreements. This exchange encompasses a wide array of information, including details about the aBLA, associated manufacturing methods, early notifications of patents that might face initial legal challenges before product launch, and presenting arguments about all potentially relevant

patents. Essentially, it facilitates multiple rounds of information exchange and allows for up to two rounds of litigation, all with the aim of expediting drug delivery to patients at a reduced cost by enabling rapid entry of biosimilars into the market.[28,29]

The patent dance process involves two phases: the first-wave patent litigation, consisting of exchanges of information, followed by the second-wave patent litigation initiated through the notice of commercial marketing.[27]

Implications of the Patent Dance

Opting out of the patent dance relinquishes the right to challenge the RPS's patents through a declaratory judgment, enabling the RPS to initiate actions regarding patent infringement, validity, or enforceability.

The RPS has control over choosing which patents to litigate, yet this might complicate assessing potential infringement risks, leading to hesitation in litigation and an increased chance of patent challenges, placing a similar burden on the aBLA applicant, particularly smaller biosimilar companies facing challenges in handling numerous identified patents.

Alternatively, if the biosimilar applicant proceeds with the patent dance, control significantly shifts to the applicant, enabling it to determine the timing and scope of the initial litigation phase by gaining insights into the RPS's relevant patent portfolio. This exchange of information mandated by the patent dance involves revealing sensitive details like potential trade secrets inherent in the biosimilar preparation process, information typically not disclosed in traditional infringement suits. Often, this process leads to parties entering into settlement agreements.

Sticking with the patent dance is advisable as it offers a systematic approach, ensuring certainty, transparency, and providing a comprehensive understanding to the applicant, RPS, and the public. This allows the biosimilar applicant to anticipate future legal expenses and make strategic litigation decisions. Additionally, if the RPS's patent portfolio is limited or weak, it can be more easily invalidated using non-infringement or invalidity defenses. Moreover, this process prevents potentially infringing products from entering the market, safeguarding the RPS's patents and preserving its market share.[29]

Effects of Inter Partes Reviews and Post-grant Review Proceedings on Biosimilar Approval (PGR)

Inter partes review, established under the America Invents Act (AIA), permits third-party challenges to patent validity based on prior art patents or printed publications in a trial conducted by administrative patent law judges. The AIA also introduced PGR allowing challenges to patents issued under the first-to-file system within nine months of issuance, encompassing additional grounds of invalidity like lack of written description or enablement. Inter partes reviews typically conclude within 18 months from the initial petition filing, including a six-month period for the Patent Trial and Appeal Board (PTAB) to decide on trial institution after the patent owner's preliminary response, and a one-year period for the PTAB to issue a final written decision if a preliminary response is filed by the patent owner.[31]

Inter partes reviews (IPRs) enable strategic challenges to patent validity, but prior declaratory judgment proceedings prevent new filings. Challengers have one year to initiate an Inter Partes Review after facing a patent infringement lawsuit, with 351(k) applicants encouraged to file early. Inter Partes Reviews lack a presumption of patent validity, requiring challengers to prove non-patentability by a preponderance of evidence under a broader claim construction standard than district courts. Recent rule changes introduce uncertainties in outcomes, and while multiple Inter Partes Reviews against a single patent are common, filing serial petitions without justification is discouraged. An unsuccessful IPR limits future challenges for both the petitioner and patent owner, making careful consideration essential.[32]

In June 2021, the USPTO updated its study on America Invents Act (AIA) trials concerning challenges to Orange Book-listed and biologic patents from September 16, 2012, through June 30, 2021. Following the introduction of post-grant proceedings, merely 4% of AIA petitions target OrangeBook patents, with a mere 2% directed at challenging biologic patents. Challenges to Orange Book patents have consistently decreased yearly since 2015, and biologic patent challenges declined from 2017 to 2020, followed by an upturn in 2021. Table 2 lists the outcomes of AIA petitions challenging Orange Book patents and biologic patents, including the outcomes of decisions on institution responsive to requests for rehearing, while joined and pending petitions are excluded. The Table 2 indicates a relatively limited focus on challenging patents within these specific categories compared to overall petition filings. The increasing count of petitions directed at biologic patents, rising from 8 petitions in FY2020 to at least 23 in FY2021, promises to offer a clearer understanding of the success rates of PTAB

Table 2 — Number and outcomes of AIA petitions during September 2012 to June 2021 challenging Orange Book and Biologic patents [34]

Outcome of the AIA petition	Number of Orange Book Patents Challenged	Number of Biologic Patents
Institution denied	175(41%)*	82(41%)
Final Written Decision (FWD)Patentable	65(15%)	14(7%)
FWD Mixed	5(1%)	7(4%)
FWD All Unpatentable	63(16%)	41(21%)
Req. Adverse Judgement	8(2%)	11(6%)
Dismissed	12(3%)	8(4%)
Settled	98(23%)	35(18%)
Total Number of Petitions	426	198

***** Figure in parenthesis indicates percentage of total petition

Table 3 — PTAB Biologics proceedings [33]

Biologic	Patent Numbers	Number of Patents Challenged	Total Inter Partes Reviews	Key Issues	Outcome
Rituximab (RITUXAN)	U.S. Patent No.8,821,873; 9,296,821; 7,820,161	10	27	Challenges included obviousness and prior art references	Two patents found unpatentable; other challenges were denied orsettled.
Trastuzumab (HERCEPTIN)	U.S. Patent No.6,407,213; 7,807,799; 7,846,441; 7,892,549	12	36	Mixed results with claims cancelled in four patents; issues included method of treatment and purification.	PTAB cancelled claims based on obviousness; some cases settled
Bevacizumab (AVASTIN)	7,807,799; 7,622,115	2	2	Challenges on methods of purification and treatment for cancer	Both patents held unpatentable as anticipated and obvious; Federal Circuit affirmed
Botulinum Toxin	10,143,728	1	1	Challenges included enablement and written description	PTAB found proposed substitute claims unpatentable for lack of written description and enablement
Adalimumab (HUMIRA)	10,155,039	1	1	Issues related to stability and claim construction regarding buffers	PTAB denied institution based on incorrect term construction; concurrent litigation settled
Filgrastim (NEUPOGEN)	9,856,287	1	1	Issues with refolding methods at high concentrations; reliance on inherency in arguments	PTAB denied institution due to inadequate expert support and reliance on inherency arguments

proceedings within the biologics sector**.** Table 3 provides an overview of PTAB biologics proceedings, detailing key cases and outcomes relevant to patent disputes in the biologics sector.[33]

It can be summarized from the table 2 that out of 624 AIA petitions, there were 426 challenging Orange Book patents and 198 challenging biologic patents. Notably, the percentage of Final Written Decisions (FWD) finding all claims unpatentable is higher for biologic patents at 21%, compared to 16% for Orange Book patents. This trend suggests that post-grant proceedings and inter partes reviews under the AIA have been particularly effective in challenging the validity of biologic patents. As a result, these proceedings may facilitate quicker approval for biosimilars by proving that certain biologic patents are unpatentable, facilitating earlier market entry for biosimilars compared to traditional patent litigation.

PTAB Proceedings

Table 3 presents cases from PTAB biologics proceedings, highlighting key details regarding

Table 4 — BPCIA lawsuits filed in 2022 and Patent Dance Participation[37]

Case Name	Reference Product at Issue	Patent dance participation	Outcomes
Regeneron v *Mylan*	Eylea (aflibercept)	Full dance	The court found that Mylan infringed Regeneron's U.S. Patent No. 11,084,865 related to Eylea.
Biogen v *Sandoz/Polpharma Biologics*	Tysabri (natalizumab)	Partial dance	Sandoz and Polpharma won FDA approval for their biosimilar
Janssen v *Amgen*	Stelara (ustekinumab)	No dance	Johnson & Johnson (J & J), the maker of Stelara (ustekinumab), has settled its lawsuit against Amgen
Genentech v *Tanvex*	Herceptin (transtuzumab)	Full dance	Genentech and Tanvex reached a settlement in principle in January 2023, and the court dismissed all claims in February 2023

patents challenged, the number of inter partes reviews (IPRs), and the outcomes of those challenges.

Selected Cases on Patent Challenges Related to Biologics and Biosimilar

Amgen v *Sandoz*

In the legal conflict between Amgen and Sandoz, revolving around biosimilar drugs, particularly Zarxio (filgrastim) and Neulasta (pegfilgrastim), significant events unfolded following the FDA's acceptance of Sandoz's biosimilar application for Zarxio, a replication of Amgen's Neupogen, on 7 July 2014. After notifying Amgen of this acceptance on July 25, 2014, Sandoz had previously communicated its anticipation of FDA approval and intentions for commercial marketing by early 2015, pursuant to regulations.

However, the situation became complex as Sandoz retracted certain offers and repeatedly reminded Amgen about its rights related to legal actions under the BPCIA. This eventually led to Amgen filing a patent infringement lawsuit about 110 days post-FDA acceptance. Notably, two prominent legal cases, Amgen v. Sandoz, highlighted contrasting approaches: Sandoz's decision not to participate in the patent dance for Zarxio led to a favorable judgment. On the other hand, following the patent dance for a proposed Neulasta biosimilar resulted in a final ruling favoring Sandoz with a non-infringement judgment. These cases revealed how strategies in engaging (or not) in the patent dance under BPCIA impacted legal outcomes in the biosimilar landscape.[35]

Amgen v *Hospira*

Following the BPCIA framework, exemplified by Amgen v Hospira, the patent dance timeline demonstrates that after FDA acceptance of Hospira's biosimilar application in late July 2019, the first patent litigation was initiated within 201 days, meeting the BPCIA requirements. The process involved sequential steps: notification triggering patent listing exchanges between parties within specific timeframes, negotiations regarding patents to litigate, and eventual agreement on litigating only one patent initially. However, with potential for more patents in subsequent litigations as per BPCIA, such as the second phase where Hospira must provide notice of commercial marketing and potential lawsuits for previously omitted patents listed in exchanges between parties, further extended litigation could ensue based on these previously identified patents, already vetted through the BPCIA framework. As Hospira's biosimilar was FDA-approved in June 2020, anticipation surrounds potential action in this second phase of litigation.[36]

Amgen v *Sanofi*

The legal dispute between Amgen and Sanofi over antibody medications targeting PCSK9 for cholesterol reduction led to the invalidation of Amgen's claims due to insufficient guidance and excessive trial and error required, emphasizing the need for specificity in patent claims and the longstanding enablement requirement for comprehensive patent disclosure.

In December 2022, the Supreme Court granted certiorari for Amgen v. Sanofi, examining the enablement standard in patent claims. Although unrelated to the BPCIA, this review questions whether a patent must instruct the use of all claim embodiments without excessive experimentation. The outcomes of this case are anticipated to generate substantial discussions and implications within the biosimilars domain in the upcoming year.[37]

The case studies highlight the effectiveness of the Biologics Price Competition and Innovation Act (BPCIA) provisions related to the patent litigation process, known as the "patent dance."

Table 4 BPCIA Lawsuits Filed in 2022 and Patent Dance Participation presents the outcomes of

litigation involving biosimilar manufacturers who participated in the patent dance compared to those who did not. Reviewing these case studies shows that participation in the patent dance often leads to more efficient resolution of patent disputes and reduces the risk of prolonged litigation. This makes it a valuable provision for balancing innovation and competition in the biologics market.

Impact of Inter Partes Reviews, PGRs, and the BPCIA on Biosimilars US Market Entry

The landscape of biosimilar market entry is significantly shaped by Inter Partes Reviews, Post-Grant Reviews, and the Biologics Control and Competition Innovation Act (BPCIA). Inter Partes Reviews have emerged as effective tools for challenging the validity of patents, often helping biosimilar manufacturers avoid lengthy litigation. As of February 28, 2023, there have been 144 biosimilar-related Inter Partes Reviews covering 70 patents and 14 reference products, indicating a proactive approach to patent disputes.

Conversely, Post-Grant Reviews have not been preferred for resolving biosimilar-related patent issues, with only few filings reported.Meanwhile, the BPCIA facilitates a structured dispute resolution process through its “patent dance,” which encourages information sharing between biosimilar manufacturers and reference product sponsors before litigation begins. Despite the complexities of patent protection, the BPCIA has not posed significant barriers to market entry for many biosimilars.

Overall, these mechanisms play a crucial role in enabling faster access to the market for biosimilars by addressing patent disputes early in the process, thus fostering a competitive environment in the biologics sector.[38]

Patenting of Biosimilars

Patent office’s grant patents to inventions meeting specific legal criteria, requiring novelty, inventiveness, and industrial applicability. Obtaining marketing approval for a biosimilar demand demonstrating high similarity to the reference product. However, patenting biosimilars poses challenges as they aim to replicate existing market products closely. Despite this challenge, patent protection may be sought for aspects like novel biosimilar preparation processes, formulations, delivery methods, dosage regimens, or new medical uses, provided they don't introduce clinically significant differences. Developers should assess potential patentable features before disclosing their biosimilar and ensure these differences don't hinder the marketing authorization application.

Biosimilars are often developed by companies as the original biopharmaceutical's patent term nears expiration (usually 20 years from the patent filing date). Innovators often rely on Supplementary Patent Protection (SPC) and Data Exclusivity to extend protection terms.[39]

Summary

The study illuminates the substantial role of IPR in the United States' biopharmaceutical landscape, crucial for fostering innovation and ensuring accessibility to affordable biologic therapies. Analyzing the BPCIA reveals its threefold function: providing regulatory pathways for approval, granting exclusivity to innovator biologics, and facilitating patent dispute resolution through the "patent dance." The 12-year post-licensure exclusivity promotes innovation but highlights the necessity of biosimilar entry for affordable healthcare.

Notably, Inter Parties Reviews serve as effective tools in assessing patent validity, aiding in resolving complex disputes. However, diverse paths to market, including litigations or settlements, have unveiled that only a few biologic patents were invalidated, showcasing Inter Partes Review’s effectiveness.

The situation is further complicated by the opportunity for originator companies to create patent thickets, which significantly delay biosimilar market entry. In the U.S., there are no caps on the number of patent applications a company can file for a single product, allowing developers to continue filing patents even long after a biologic has been launched. This practice leads to patent thickets, where multiple overlapping and often low-quality patents are filed to extend market exclusivity beyond the original patent expiration. AbbVie's Humira exemplifies this issue, with a U.S. patent portfolio containing over 70 duplicative patents, compared to just eight non-duplicative patents in the EU. AbbVie asserted 63 of these patents against a single biosimilar manufacturer, delaying competition and access to more affordable treatments.

This disparity is largely fueled by the incentives embedded within the U.S. patent system. Patent examiners at the U.S. Patent and Trademark Office

(PTO) are incentivized to grant patents, contributing to an environment where anti-competitive practices thrive. The high prevalence of patent thickets, supported by lenient standards on functional claims and broad patent specifications, continues to delay biosimilar availability, increasing healthcare costs.

Policy interventions are essential to address these issues. The U.S. could adopt stricter scrutiny on functional claims and more comprehensive patent specifications, similar to the European model, which imposes tighter restrictions on patent thickets. This would help prevent unnecessary market exclusivity extensions that obstruct biosimilar competition.

Conclusion

The IPR landscape surrounding biosimilars has profound implications for various stakeholders, including patients, innovators, regulators, and biosimilar manufacturers. For patients, the protection of IPR on biologics delays the entry of cost-effective biosimilars, resulting in higher healthcare costs, particularly in the context of life-threatening diseases where many biologics serve as critical therapies, such as anticancer treatments. The current U.S. patent landscape, characterized by patent thickets and secondary patenting, creates significant barriers to biosimilar entry, allowing originator biologic manufacturers to maintain monopolies on their products and leading to exorbitant costs for patients and healthcare systems. Innovators rely on IPR protection to recoup the substantial investments made in developing biologics, and without sufficient protection, there could be a disincentive for further innovation. Regulators are faced with the challenge of striking a delicate balance between encouraging innovation through patent protection and ensuring affordable access to life-saving medications. Biosimilar manufacturers, on the other hand, encounter significant hurdles due to the legal and regulatory barriers imposed by innovators, particularly in cases of "evergreening" patents, which extend monopolies on biologics and complicate the approval process. Stricter patentability standards should be implemented to reduce extensive patent protections that stifle competition and delay access to affordable treatments, as research indicates that biosimilars can provide significant cost savings potentially reducing prices by 15% to 35% compared to their reference products thereby increasing patient access to essential therapies. Additionally, Price regulations should be implemented for innovator biologics to protect innovation while maintaining fair prices during the patent period. This approach aims to enhance public access to effective biological therapies at affordable rates.The passage of President Biden's Inflation Reduction Act (IRA), which allows the federal government to negotiate drug prices for Medicare starting in 2026, may also indirectly support biosimilar market growth. The IRA targets biologics that have been on the market for over 13 years, and branded products may seek exemptions only if a biosimilar is expected to launch within two years. This act has the potential to lower costs, but its impact on biosimilar market dynamics remains to be seen.

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